Convenient Synthesis of 3-Aminocoumarin Derivatives by the Condensation of 1,4-Diacetyl- or 3-Substituent-2,5-piperazinediones with Various Salicylaldehyde Derivatives

Chung-gi SHIN,* Yoshiharu NAKAJIMA, Toshiya HAGA, and Yoshiaki SATO
Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221
(Received June 17, 1986)

The condensation of 1,4-diacetyl- or 3-substituted 2,5-piperazinediones (PDO) with various salicylaldehyde derivatives in the presence of a base, such as potassium *t*-butoxide or triethylamine, was found to give two extremely different kinds of products: 1-acetyl-3-arylmethylene-PDO and 3-(acylamino)coumarin derivatives. The former, which has a (*Z*)-geometric structure, was readily converted to the latter by irradiation. Furthermore, the conversion mechanism and the structural confirmation are discussed.

In a previous paper,[1] we briefly reported on the synthesis of a (*Z*)-3-salicylidene-2,5-piperazinedione derivative (**2a**; 2,5-piperazinedione=PDO), which was supposed to be the most promising precursor for the synthesis of spiro[benzofuran-2(3*H*), 2′-piperazine]-3′,6′-dione as the main skeleton of aspirochlorin.[2,3] In addition, interestingly enough, a similar reaction of 1,4-diacetyl-PDO (**1**) with salicylaldehyde gave an unexpected 3-aminocoumarin derivative **3a** along with **2a**, which was found to be further converted to **3a** upon irradiation. However, in regard to the synthesis of 3-(acylamino)coumarin from α-amino acid derivatives, at present only a few synthetic methods have been reported.[4-6]

In the present paper we wish to report on details regarding the facile and convenient syntheses of several kinds of 3-(acylamino)coumarin derivatives by the condensation of **1**, (3*S*)-1,4-diacetyl-3-alkyl-PDO (**4**) or 4-substituted (*Z*)-1-acetyl-3-alkylidene-PDO (**7**) with various salicylaldehyde derivatives, followed by the irradiation. Furthermore, the mechanism of the photochemical conversion and the structural confirmation of all the new compounds are also discussed.

Results and Discussion

Condensation of 1,4-Diacetyl-PDO with Salicylaldehydes. According to the Gallina and Liberatori method,[7] the condensation of equimolar **1** with salicylaldehyde in the presence of potassium *t*-butoxide was performed to give 1-acetyl-3-(2-hydroxybenzylidene)-PDO (**2a**) and 3-(*N*-acetylglycylamino)coumarin (**3a**) derivatives in a 53 and a 40% yields, respectively. As was previously reported,[1] the structure of **3a** could be readily determined by the conversion of **3a** with 1 M† HCl to the authentic 3-hydroxycoumarin; this was completely consistent with the product derived by the hydrolysis of known 3-(acetylamino)coumarin with 1 M HCl.

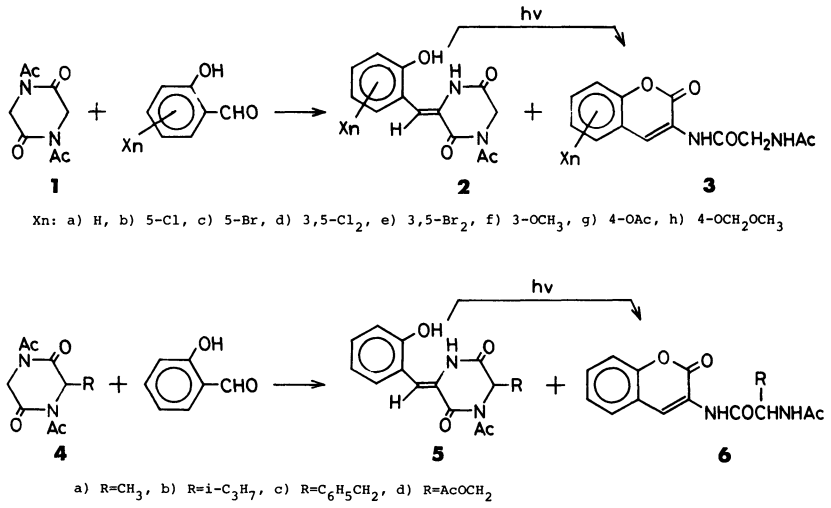
Furthermore, in order to generallize the synthesis of 3-(acylamino)coumarin (**3**) derivatives, first a similar condensation of **1** with several mono- and disubstituted 2-hydroxybenzaldehydes (**b**; X_1=5-Cl, **c**; X_1=5-Br, **d**; X_2=3,5-Cl_2, **e**; X_2=3,5-Br_2, **f**; X_1=3-OCH_3, **g**; X_1=4-$OCOCH_3$, **h**; X_1=4-OCH_2OCH_3) in *N*,*N*-dimethylformamide (DMF) at 10 °C was carried out, as shown in Scheme 1. As a result, both 1-acetyl-3-(2-hydroxyarylidene)-PDO (**2b—h**) as main products and 3-(*N*-acetylglycylamino)coumarin derivatives **3b—h** were also obtained in good yields. However, in the case of the reaction of **1** with 2-hydroxy-3-methoxybenzaldehyde (**f**), it was found that a similar condensation ultimately took place in the presence of two molar potassium *t*-butoxide to give only 3-(2-hydroxy-3-methoxybenzylidene)-PDO (**2f**) in a 30% yield not accompanied by the corresponding 3-aminocoumarin derivative **3f**. On the other hand, a similar reaction in the presence of equimolar triethylamine instead of potassium *t*-butoxide was found to give **2f** and **3f** in a 80 and a 16% yields, respectively. In addition, the analogous condensation of **1** with 2-hydroxy-4-(methoxymethoxy)benzaldehyde (**h**) was also carried out to give the corresponding 3-benzylidene-PDO (**2h**) and 3-aminocoumarin derivatives **3h** in a 43 and a 21% yields, respectively.

The reaction conditions of the above several condensations and the ratio of the yield of products **2** and **3** are summarized in Table 1.

Subsequently, compounds **2b—h** were irradiated in methanol with a high-pressure mercury lamp (500 W) under a stream of N_2 gas at room temperature to give **3b—h** in almost quantitative yields. In addition, it was found that the condensation products obtained as a mixture of **2** and **3** were in situ also irradiated to give only **3**. In both cases, the photochemical conversion of **2** to **3** was completed in less than 1 h.

Furthermore, in order to develop the above consecutive reaction and to investigate the asymmetric addition to the aminocoumarin derivatives containing a chiral α-amino acid residue, the other 1,4-diacetyl-PDO derivatives **4** and **7** as substrates were chosen and subjected to a similar condensation, followed by the irradiation. The optically active PDO (**4**: **a**; R=CH_3, **b**; R=*i*-C_3H_7, **c**; R=$C_6H_5CH_2$, **d**; R=CH_3-$COOCH_2$) were similarly condensed with salicylalde-

† 1 M=1 mol dm^{-3}.



Scheme 1.

Table 1. Reaction Conditions of the Condensation and Yield Ratio of the Products **2** and **3**

(2-Hydroxy)arylaldehyde Substituent Xn	Base (equiv) *t*-BuOK (Et3N)	Yield/% **2**	**3**	Ratio (**2**/**3**)
—	1	53	40	1.3
5-Cl	1	73	19	4.0
5-Br	1	80	20	4.0
3,5-Cl_2	1	70	18	4.0
3,5-Br_2	1	54	26	2.0
3-OMe	1	0	0	—
3-OMe	2	30	0	—
3-OMe	(1)	80	16	5.0
4-OAc	1	30	10	3.0
4-OCH_2OMe	(1)	43	21	2.0

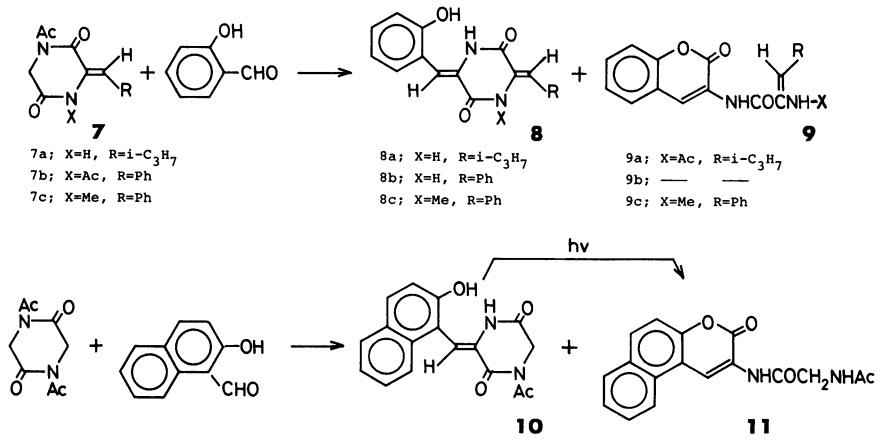
hyde to give the desired 1-acetyl-6-alkyl-3-salicylidene-PDO (**5a—d**) and 3-[α-(acetylamino)acylamino]-coumarin derivatives **6a—d** in 49—64 and 16—25% yields, respectively. In an analogous manner as in the case of **2**, the subsequent irradiation of **5a—d** were also converted to **6a—d** within 1 h, as illustrated in Scheme1.

On the other hand, in the case of 3-alkylidene-PDO derivatives **7**, for example, 1-acetyl-3-isobutylidene-(**7a**), 1,4-diacetyl-3-benzylidene-(**7b**), and 1-acetyl-3-benzylidene-4-methyl-PDO (**7c**) were found to not react at all when the Gallina and Liberatori method[7] was used. However, according to the Sasaki method,[8] compounds **7a—c** reacted with 2.5 mole of salicylaldehyde in the presence of 4 mole of anhydrous sodium acetate in acetic anhydride under reflux for 8 h to give the corresponding 3-alkylidene-6-salicylidene-PDO derivatives **8a—c** in 60—74% yields as the main products along with a very small amount of 3-(α-acetylamino-α-alkylideneacetylamino)coumarins **9a, c** in low yields. As shown in Scheme 2, in the case of **7b**, the by-product **9b** could not be obtained at all. Unfortunately, it was found that not only increasing the yield of **9** by even the modified Sasaki method but also the photochemical conversion of **8** to **9** was unsuccessful.

The yields, physical constants, and the spectral (IR and ^1H NMR) data of **2, 3, 5, 6, 8,** and **9** are summarized in Tables 2—5, and 6.

In order to further extend the above sequential reactions, another type of aromatic aldehyde was explored as an alternative to the salicylaldehyde derivatives. For example, the condensation of **1** with 2-hydroxy-1-naphthaldehyde in the presence of potassium *t*-butoxide was carried out in order to give the expected (*Z*)-1-acetyl-3-(2-hydroxy-1-naphthylmethylene)-2,5-piperazinedione (**10**) and 2-(*N*-acetylglycylamino)-3*H*-naphtho[2,1-*b*]pyran-3-one (**11**) in a 50 and a 20% yields, respectively. Subsequently, the former **10** was also converted in quantitative yield to **11** by irradiation. As a result, it could be concluded that the aromatic aldehyde having a vicinal hydroxyl group was applicable to the above successive condensation with PDO derivatives and irradiation.

Conversion Mechanism. For the purpose of the investigating the photochemical conversion mechanism of **2** to 3-aminocoumarin derivatives, in particular, (*Z*)-**2a** was subjected to geometric isomerization; this is because it was assumed that **2a** isomerized to (*E*)-isomer, followed immediately by a conversion to



Scheme 2.

Table 2. The Yields and Physical Constants of **2**

Compd No.	Mp θ_m/°C[a)]	Formula	Found (Calcd) (%)			IR, ν/cm^{-1} in KBr		^{1}H NMR, δ in DMSO-d_6	
			C	H	N	NH (OH)	C=C	NH (OH)	-CH=
2a	200—201	$C_{13}H_{12}N_2O_4$	60.37 (59.99	4.60 4.65	10.82 10.77)	3070 (3380)	1630	10.00bs (10.56bs)	7.03s
2b	214—216	$C_{13}H_{11}N_2O_4Cl$	53.01 (52.97	3.70 3.74	9.49 9.52)	3100 (3400)	1630	8.60bs (9.80bs)	7.01s
2c	208—210	$C_{13}H_{11}N_2O_4Br$	46.05 (46.02	3.09 2.95	8.26 8.26)	3100 (3400)	1630	8.06bs (9.92bs)	7.08s
2d	221—222	$C_{13}H_{10}N_2O_4Cl_2$	47.61 (47.42	2.96 3.04	8.28 8.51)	3100 (3300)	1640	8.64bs (10.10bs)	7.00s
2e	255—256	$C_{13}H_{10}N_2O_4Br_2$	37.21 (37.34	2.31 2.40	6.48 6.70)	3050 (3300)	1635	8.54bs (9.90bs)	6.98s
2f	216—217	$C_{14}H_{14}N_2O_4$	57.82 (57.92	4.71 4.86	9.62 9.65)	3100 (3200)	1635	6.8—7.2m (Ph) (9.90b)	
2g	191—192	$C_{15}H_{14}N_2O_6$	56.19 (56.05	4.43 4.35	8.80 8.65)	3380	1630	6.6—7.6m (Ph)	6.72s
2h	192—193	$C_{15}H_{16}N_2O_6$	56.19 (56.04	4.86 4.75	8.71 8.98)	3400	1630	6.3—7.6m (Ph) (10.02bs)	

a) Colorless needles from methanol.

Table 3. The Yields and Physical Constants of **3**

Compd[a)] No.	Mp θ_m/°C[b)]	Formula	Found (Calcd) (%)			IR ν/cm^{-1} in KBr			^{1}H NMR, δ in $CDCl_3$		
			C	H	N	NH	NCO	C=C	-NHCO-	-CH_2NH- (J_{Hz})	-CH=
3a	213—214	$C_{13}H_{12}N_2O_4$	60.99 (60.98	4.64 4.68	10.77 10.88)	3315	1690 1535	1620	9.64bs	8.33t (5.5)	8.57s
3b	224—226	$C_{13}H_{11}N_2O_4Cl$	52.62 (52.97	3.44 3.74	9.35 9.52)	3300	1680 1530	1630	10.26bs	8.55t (5.5)	6.90s
3c	235—236	$C_{13}H_{11}N_2O_4Br$	46.04 (46.03	3.09 2.95	8.23 8.26)	3300	1680 1530	1630	9.69bs	8.32t (6.0)	7.00s
3d	232—233	$C_{13}H_{10}N_2O_4Cl_2$	47.32 (47.42	2.88 3.04	8.47 8.51)	3300	1680 1540	1630	9.96bs	8.36t (6.0)	7.46s

Table 3. (Continued)

Compd[a] No.	Mp θ_m/°C[b]	Formula	Found (Calcd) (%)			IR ν/cm^{-1} in KBr			^{1}H NMR, δ in $CDCl_3$		
			C	H	N	NH	NCO	C=C	-NHCO-	$-CH_2NH-$ (J_{Hz})	-CH=
3e	259—260	$C_{13}H_{10}N_2O_4Br_2$	37.52 (37.34	2.30 2.40	6.64 6.70)	3300	1680 1540	1630	10.02bs	8.26t (6.0)	6.94s
3f	248—249	$C_{14}H_{14}N_2O_5$	57.90 (57.92	4.77 4.86	9.65 9.65)	3300	1680 1540	1630	8.38bs	8.32t (6.0)	6.70—7.60 (Ph)
3g	223—224	$C_{15}H_{14}N_2O_6$	56.20 (56.04	4.43 4.35	8.80 8.65)	3375 3275	1690 1515	1630	9.69bs	8.32t (6.0)	7.28s
3h	199—200	$C_{15}H_{16}N_2O_6$	56.24 (56.04	4.73 4.43	8.74 8.67)	3370 3300	1680 1540	1630	9.64bs	8.36t (6.0)	7.10s

a) Almost quantitative yield from **2** by the irradiation. b) Colorless needles from methanol.

Table 4. The Yields and Melting Points of **5** and **6**

Compd No.	Yield %	Mp θ_m/°C	Formula	Found (Calcd) (%)		
				C	H	N
5a	64	135—136[a]	$C_{14}H_{14}N_2O_4$	60.99 (61.31	5.15 5.15	9.81 10.21)
5b	62	85—86[a]	$C_{17}H_{20}N_2O_4$	64.25 (64.54	6.79 6.37	8.81 8.86)
5c	54	syrup	$C_{20}H_{18}N_2O_4$	68.20 (68.56	5.00 5.18	7.74 8.00)
5d	49	syrup	$C_{16}H_{16}N_2O_6$	57.49 (57.83	4.58 4.85	8.11 8.43)
6a	22	195—196[b]	$C_{14}H_{14}N_2O_4$	61.02 (61.31	5.20 5.15	9.90 10.21)
6b	16	186—187[c]	$C_{17}H_{20}N_2O_4$	64.32 (64.54	6.25 6.37	8.61 8.86)
6c	25	241—242[d]	$C_{20}H_{18}N_2O_4$	68.20 (68.56	5.20 5.18	8.06 8.00)
6d	24	172—173[e]	$C_{16}H_{16}N_2O_6$	57.82 (57.83	4.85 4.85	8.63 8.43)

a) Colorless needles from cyclohexane. b) Colorless needles from benzene. c) Colorless needles from CCl_4. d) Colorless needles from methanol. e) Colorless needles from ethanol.

Table 5. The Spectral and Optical Data of **5** and **6**

Compd No.	IR, ν/cm^{-1} in KBr NH	C=C	-OH, -NHCH- (J_{Hz})	^{1}H NMR, δ in $CDCl_3$ -NHCO-	-CH= [Ph+H]	-CH-R (J_{Hz})	$[\alpha]_D^{25}$ (c 1.0) in MeOH
5a	3150	1630	10.56bs	7.14bs	[6.84—7.44m]	5.15q (7.3)	−154.4°
5b	3180	1635	10.75bs	7.16bs	[6.84—7.42m]	6.27t (6.0)	−31.6°
5c	3175	1630	10.76bs	10.56bs	[7.10—7.80m]	4.40t (5.0)	−120.0°
5d	3370	1630	10.46bs	7.16bs	[6.80—7.80m]	5.36t (4.0)	−80.4°

Table 5. (Continued)

Compd No.	IR, ν/cm^{-1} in KBr NH	C=C	^{1}H NMR, δ in CDCl$_3$ -OH, -NHCH- (JHz)	-NHCO-	-CH= [Ph+H]	>CH-R (JHz)	$[\alpha]_D^{25}$ (c 1.0) in MeOH
6a	3275	1630	8.32d (8.0)	9.60bs	8.56s	4.60t (8.0)	−120.7°
6b	3350	1635	6.67d (7.5)	8.90bs	8.64s	7.78t (8.0)	−92.5°
6c	3300	1635	8.36d (8.0)	9.84bs	8.60s	4.90m	−146.1°
6d	3325	1635	8.24d (8.0)	9.75bs	8.56s	4.92m	−105.5°

Table 6. The Yields and Physical Constants of **8** and **9**

Compd No.	Yield %	Mp[a] θ_m/°C	Formula	Found (Calcd) (%) C	H	N	IR, ν/cm^{-1} in KBr NH (OH)	C=C	^{1}H NMR, δ[b] -OH	-CH= (JHz)
8a	60	176—177	$C_{15}H_{16}N_2O_3$	66.02 (66.16	6.21 5.92	10.08 10.29)	3080 (3400)	1630	10.18	5.66d (10.00)
8b	72	270—271	$C_{17}H_{14}N_2O_3$	69.31 (69.37)	4.92 4.80	9.39 9.52)	3160 (3400)	1630	10.10	6.6—7.6m (+Ph)
8c	74	175—176	$C_{19}H_{16}N_2O_3$	71.33 (71.24)	5.12 5.03	8.64 8.75)	3150 (3400)	1630	10.56	6.6—7.3m (+Ph)
9a	3	203—204	$C_{15}H_{16}N_2O_3$	65.98 (66.16	6.11 5.92	10.33 10.29)	3325	1630	—	?
9c	3	154—155	$C_{19}H_{16}N_2O_3$	71.22 (71.24	4.87 5.03	8.95 8.75)	3300 3325	1630	—	7.1—7.5m (+Ph)

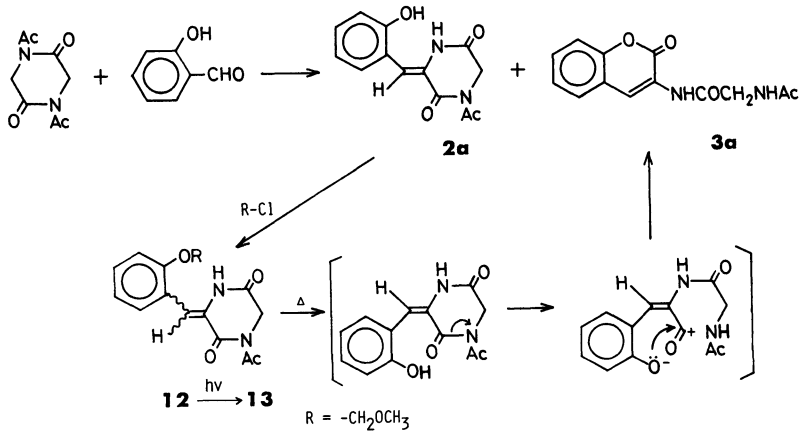
a) Colorless needles from cyclohexane. b) Recorded in DMSO-d_6.

the coumarin derivative **3a**. Accordingly, firstly, in order to confirm the resulting isomerization and to prevent the transformation, *o*-hydroxyl group of 3-salicylidene in **2a** was protected with methoxymethyl (MOM) chloride by the usual method to give (*Z*)-1-acetyl-3-[(*O*-MOM)salicylidene]-PDO (**12**) in good yield. Subsequently, the photochemical conversion of **12** with a high-pressure Hg lamp (500 W) gave the expected (*E*)-1-acetyl-3-[(*O*-MOM)salicylidene]-PDO (**13**) in ca. a 40% yield. The configurational structure of **13**, thus obtained, was readily confirmed by a comparison with both chemical shifts of the olefin protons between the two geometric isomers. Generally, it is well-known that the olefin proton of α,β-unsaturated α-amino acid and its cyclic dipeptide of (*E*)-isomer shift at a higher magnetic field than that of (*Z*)-isomer.[9-11] In fact, it was found that the olefin proton of (*E*)-isomer **13** shifted at a higher magnetic field (δ 6.62) than that of (*Z*)-isomer **12** (δ 7.10) by ca. $\Delta\delta$ 0.48. The subsequent deprotection of **13** with a saturated HCl methanol solution at room temperature gave the desired **3a**, as illustrated in Scheme 3. From this result, it could by readily determined that, after the photochemical isomerization of **12** to **13** and subsequent deprotection of **13**, the PDO ring of the unstable intermediate (*E*)-1-acetyl-3-salicylidene-PDO [(*E*)-**2**], thus obtained, easily cleaved and a simultaneous nucleophilic addition of the resulting *o*-hydroxyl group to the neighboring carbonyl group took place to form **3**.

In conclusion, the conversion mechanism could be confirmed unambigously that the condensation of **1**, **4**, or **7** with salicylaldehyde derivatives yielded a mixture of (*Z*)- and (*E*)-isomers during the first step, the latter of which was immediately transformed by a successive ring cleavage and then recyclized to give **3**, **6**, **9**, and **11**.

Experimental

General. Melting points were determined with a Yamato micro melting-point apparatus model MP-21 and were uncorrected. The IR spectra were recorded with a Hitachi EPI-G2 grating spectrometer. The ^{1}H NMR spectra were measured with a JEOL JMN PS-100 spectrometer in a CDCl$_3$ solution with tetramethylsilane as the internal standard. The specific rotations were measured in a 0.5-dm tube using a JASCO DIP-4 polarimeter (Japan Spectroscopic Co. Ltd.).



Scheme 3.

Condensation of 1 with Salicylaldehyde Derivatives. General Procedure. To a solution of **1** (19.8 g, 100 mmol) and an appropriate salicyladehyde (110 mmol) in DMF (260 ml) was added 1.1 mole of 0.5 M potassium *t*-butoxide, with stirring, drop-by-drop at 0 °C for 1 h. After the addition, the solution was continuously stirred at room temperature for 12 h and neutralized with acetic acid. It was then poured into ice-water (100 ml). A colorless crystalline deposited substance was collected and recrystallized from methanol to give two kinds of colorless needles. Repeated recrystallization from methanol gave pure **2** as colorless needles. On the other hand, after concentrating the mother liquor, the residual crystalline mixture was then chromatographed on a silica-gel column using a mixture of benzene and acetone (40 : 1 v/v) as the eluent to give two fractions. The main fraction was evaporated under reduced pressure to give residual crystals, which were also recrystallized from methanol to give **3** as colorless needles.

In the case of reactions with 3-methoxy- and 4-(*O*-MOM)-salicylaldehyde, a similar condensation was worked up in the presence of triethylamine, instead of potassium *t*-butoxide (See Table 1).

Irradiation of 2. A solution of **2** (0.1 mmol) in methanol (50 ml) was irradiated with a 500-W high-pressure mercury lamp under a N_2 gas stream at room temperature. The photochemical conversion of **2** was terminated within 1 h. The solution was concentrated under reduced pressure to give residual crystals which were subsequently recrystallized from methanol to give **3**.

Condensation of 4 with Salicylaldehyde. In a similar manner as in the case of **1**, the treatment of **4** (9.35 mmol) with 1.1 equivalent of salicylaldehyde (10.30 mmol) in the presence of 0.5 M potassium *t*-butoxide was worked up for 30 min to give **5** and **6** as colorless needles.

Irradiation of 5. A solution of **5** (0.1 mmol) in methanol (50 ml) was similarly irradiated to give **6**.

Condensation of 7 with Salicylaldehyde. A solution of **7** (20 mmol) and salicylaldehyde (6.1 g, 50 mmol) in acetic anhydride (29 ml) in the presence of anhydrous sodium acetate (6.5 g, 79 mmol) was refluxed for 8 h. After removing excess acetic anhydride under reduced pressure, the residue was dissolved in ethyl acetate (200 ml) and the solution was washed once with 1 M hydrochloric acid and once with a saturated sodium chloride aqueous solution and then dried over anhydrous magnesium sulfate. The removal of the solvent under reduced pressure gave colorless crystals which comprised two chemical species. Subsequent separation by chromatography on a silica-gel column using a mixture of chloroform and acetone (30 : 1 v/v) as the eluent afforded two fractions. The first fraction was concentrated under reduced pressure to give **8** and the second gave **9** as colorless needles (See Table 6).

Condensation of 1 with 2-Hydroxy-1-naphthaldehyde. To a mixture of **1** (5.0 g, 28.1 mmol) in DMF (80 ml) was slowly added triethylamine (3.4 g, 33.6 mmol), with stirring, at −10 °C. After stirring at room temperature for 16 h, the reaction solution was neutralized to pH 7 with 3 M HCl under cooling and then diluted with water (300 ml). The solution was extracted three times with ethyl acetate (300 ml) and the combined extracts were dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the obtained residual syrup was gradually solidified to give crude crystals; these were collected after adding diisopropyl ether. Recrystallization from acetone gave yellowish fibrous solid as a mixture of **10** and **11**, which were did not separated. However, based on the ^{1}H NMR spectrum, the ratio of yield was found to be 4 : 1 (**10** : **11**).

Preparation of 11. The above mixture (300 mg) in methanol (70 ml) was irradiated with a 500-W high-pressure Hg lamp under a N_2 gas stream at room temperature for 3 h. The mixture gradually dissolved to give a homogeneous solution. The removal of methanol gave a crude crystalline substance, which was recrystallized from acetone to give **11** as a pale-yellow fibrous solid. Mp 250 °C (decomp). ν_{max}^{KBr} (cm^{-1}) 3200 (NH), 1685, 1530 (NHCO), 1650 (C=C); ^{1}H NMR (DMSO-d_6) δ=9.79 (bs, 1H, NH), 9.27 (s, 1H, -CH=), 8.35 (t, 1H, J=6.0 Hz, NH), 4.10 (d, 2H, J=6.0 Hz, -CH_2-). Found: C, 65.93; H, 4.41; N, 8.97%. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03%.

Preparation of 12. To a solution of **2a** (3 g, 11.5 mmol) in tetrahydrofuran (45 ml) in the presence of triethylamine (1.28 g, 12.6 mmol) was slowly added chloromethyl methyl ether (1.21 g, 15.0 mmol) with stirring at 0 °C for 1 h. The deposited salt was filtered off and the filtrate was concentrated under reduced pressure. The residual crystals, thus obtained, were collected and then recrystallized from ethyl acetate to give **12** as colorless needles. Yield 82%, mp 137—138 °C. ν_{max}^{KBr} (cm^{-1}) 1725, 1700 (C=O), 1620 (C=C); ^{1}H NMR δ=10.1 (bs, 1H, NH), 7.10 (s, 1H, -CH=), 4.35 (s, 2H, -CH_2-). Found: C, 59.15; H, 5.28; N, 9.16%. Calcd for $C_{15}H_{16}N_2O_5$: C,

59.20; H, 5.30; N, 9.21%.

Preparation of 13. A solution of **12** (1.49 g, 4.9 mmol) in methanol (70 ml) was irradiated with a 500-W high-pressure Hg lamp under a N_2 gas stream at room temperature for 8 h. Insoluble materials separeted out were filtered off and then the filtrate was concentrated under reduced pressure to give a crystalline residue. The crystals, thus obtained, were purified on a silica-gel column using a mixture of chloroform and acetone (20 : 1 v/v) as the eluent. After concentration of the fraction, the obtained crystals were recrystallized from carbon tetrachloride to give **13** as colorless needles. Yield 33%, mp 85—86 °C. ν_{max}^{KBr} (cm^{-1}) 3040 (NH), 1630 (C=C); ^1H NMR δ=10.62 (bs, 1H, NH), 4.30 (s, 2H, $-CH_2-$). Found: C, 58.99; H, 5.27; N, 9.17%. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.21%.

Conversion of 13 to 3a. A solution of **13** (110 mg, 0.38 mmol) in methanol (10 ml) was stirred below 0 °C. To the solution was added a methanol solution (10 ml) saturated with hydrogen chloride gas. After stirring for 2 h and then removing the solvent, the obtained residue was purified on a silica-gel column using a mixture of chloroform and methanol (10 : 1 v/v) as the eluent to give **3a** in a 70% yield.

References

1) C. Shin, Y. Nakajima, and Y. Sato, *Chem. Lett.*, **1984**, 1301.

2) K. Sakata, H. Masago, A. Sakurai, and N. Takahashi, *Tetrahedron Lett.*, **23**, 2095 (1982).

3) D. Brewer, A. G. McInnes, D. G. Smith, A. Taylor, and J. A. Walter, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1248.

4) A. E. EL-Naggar, F. T. M. Ahmed, A. M. Abd El-Salam, M. A. Radi, and M. S. A. Latif, *J. Heterocycl. Chem.*, **18**, 1203 (1981).

5) L. Jurd, A. D. King. Jr., and K. Mihara, *Photochemistry*, **10**, 2965, 2971 (1971).

6) R. Walter, T. C. Purecelly, and H. Zimmer, *J. Heterocycl. Chem.*, **3**, 235 (1966).

7) C. Gallina and A. Liberatori, *Tetrahedron*, **1974**, 664.

8) T. Sasaki, *Chem. Ber.*, **54**, 163 (1921).

9) A. Srinivasan, K. D. Richards, and R. K. Olsen, *Tetrahedron Lett.*, **1976**, 891.

10) D. Hoppe and R. Follmann, *Chem. Ber.*, **109**, 3062 (1976).

11) C. Shin, M. Hayakawa, T. Suzuki, A. Ohtsuka, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **51**, 550 (1978).